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Research Article

The relationship between neutrophil–lymphocyte ratio and in-stent restenosis in superficial femoral artery

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The present study aimed to investigate the relationship between an increase in the pre- and post-operative neutrophil–lymphocyte ratio (NLR) and superficial femoral artery in-stent restenosis (ISR) rate. We recruited 199 patients that underwent superficial femoral artery stenting for lower extremity arteriosclerosis obliterans at our hospital from March 2015 to July 2018. Patients were divided into two groups according to the occurrence of ISR within 1 year (group 1, ISR and group 2, Non-ISR). The after NLR (NLR_{after}) and NLR change ratio (NLR_{ratio}) ($P<0.001$) were significantly higher in group 1. A $NLR_{after} > 4.3$ was associated with an odds ratio of 1.946 (95% CI [1.51–2.50]; $P<0.001$) for the presence of ISR. A $NLR_{ratio} > 37.5\%$ was associated with an odds ratio of 3.6 (95% CI [2.03–6.36]; $P<0.001$) for occurrence of ISR. A NLR_{after} level > 4.3 had 75% sensitivity and 76% specificity for the prediction of ISR, as identified by the ROC curve. A NLR_{ratio} level $> 37.5\%$ predicted ISR with 77% sensitivity and 60% specificity. Multivariate logistic regression analysis demonstrated that NLR_{ratio} was the strongest independent predictor of ISR ($P<0.001$). In conclusions, NLR_{ratio} could be used as a prognostic marker in superficial femoral artery stents.

Introduction

Arteriosclerosis obliterans of the lower limbs is caused by the formation of atherosclerotic plaques of the lower limbs, which leads to arterial stenosis and occlusion, leading to chronic limb ischemia. Percutaneous superficial femoral interventions are the preferred treatment for superficial femoral artery disease, even though the occurrence of in-stent restenosis (ISR) continues to be an important complication [1,2]. The mechanism of stent restenosis is unclear. Neointimal proliferation underlies the pathophysiological development of ISR and is triggered by the pro-inflammatory molecules released due to endothelial damage, particularly during the thrombogenic and proliferative phases of ISR [3].

Recent studies have shown that inflammatory processes play an important role not only in the occurrence and development of atherosclerosis, but also in the occurrence of ISR [4,5]. The neutrophil–lymphocyte ratio (NLR) has been shown to be a marker of inflammation and closely related to increased cardiovascular mortality and morbidity [6,7]. Although the relationship between various inflammatory biomarkers, including NLR, and the occurrence of ISR has been investigated [8–10]. No studies have evaluated the effectiveness of the NLR value after (NLR_{after}), NLR change(NLR_{change}), defined as the NLR value before (NLR_{before}) and after (NLR_{after}) superficial femoral artery stenting (SFAS) intervention and NLR change ratio (NLR_{ratio}), defined as the ratio of NLR_{change} to NLR_{before}, in prediction of ISR in superficial femoral artery stents, which are at high risk for the occurrence of ISR. The present

study aims to investigating the relationship between an increase in the pre- and post-operative NLR and superficial femoral artery ISR rate.

Patients and methods
Patient selection and research design

We recruited 199 patients that underwent SFAS for lower extremity arteriosclerosis obliterans at our hospital from March 2015 to July 2018. Inclusion criteria included the following: 1. Adult patients that underwent successful percutaneous transluminal stent implantation for superficial femoral artery lesions; 2. TASC-II classification of the femoral artery [1]: TASC-IIA, TASC-IIB, and TASC-IIC patients; 3. At least one arterial run-off below the knee, although stenosis lesions that were not limiting the flow may be included; 4. No evidence of residual inflow problems in the aortoiliac artery, although stenosis lesions that were not limiting the flow may be included. Exclusion criteria included the following: 1. Evidence of contraindications to anti-coagulation; 2. Active infection, chronic inflammatory disease, malignancy and chronic obstructive pulmonary disease; 3. evidence of hematological disease; 4. Presence of severe cardiac insufficiency (New York Heart Association grade III or IV), liver dysfunction (Child grade B or C) or renal insufficiency (creatinine clearance < 30 ml/min); and 5. No arterial run-off below the knee. All patients donated venous blood 3 days before and then after implantation. Routine hematological parameters including monocyte count, eosinophil count, basophil count, platelet count, platelet distribution width, neutrophil count, lymphocyte count, and levels of triglycerides, cholesterol, high-density lipoprotein, low-density lipoprotein, Bilirubin, Albumin, were measured by an auto-analyzer (Model XE2100; Sysmex Co, Kobe, Japan). Clinical and demographic data, and laboratory results were obtained from the hospital electronic medical records system for admitted patients. Hypertension was defined as blood pressure $\geq 140/90$ mm/Hg or treatment with anti-hypertensive medications. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dl or treatment with oral anti-diabetic drugs or insulin. Smokers were defined as current cigarette users or patients who had quit smoking within 1 month of the procedure.

Before the procedure, patients received dual anti-platelet therapy consisting of aspirin (100 mg/d) plus clopidogrel (75 mg/d). The contralateral cross-over approach was used for all procedures. Interventional operations were performed through a 5F or 6F sheath (length 11–45 cm). Selective angiography was performed to localize lesions and measure the range of lesions by using 4F or 5F catheter. Balloon angioplasty was performed using the predilatation technique, and the diameter of balloon was determined by angiography. Self-expanding stents were implanted with a residual diameter stenosis $> 30\%$ and/or flow-limiting dissection after balloon angioplasty in accordance with American College of Cardiology/American Heart Association guidelines [11]. Self-expanding stents had a diameter of 6 mm, and 5-mm diameter balloons were used for postdilatation within the stent. Percutaneous transluminal angioplasty success was defined as dilation of all arterial lesions with a residual stenosis of 20%. Stent technical success was defined as a residual stenosis of $< 20\%$ after stent placement. All interventional procedures were performed under local anesthesia. All patients received 5000 units of heparin during the procedures. After taking 100 mg of aspirin and clopidogrel at 75 mg for 12 months, clopidogrel was discontinued and administration of aspirin was sustained. Doppler ultrasonography, computed tomography angiography or digital subtraction angiography was performed every 3–6 months after stenting the superficial femoral artery. ISR was defined as not less than 50 percent stenosis in the treated lesion [12]. The study was approved by the local Ethics Committee of the Fourth Affiliated Hospital of China Medical University. All patients signed an informed consent.

Statistical analysis

Data were analyzed using the SPSS version 21.0 software package. Continuous data were given as mean $\pm$ S.D. Discrete parameters were presented as percentages. The Kolmogorov–Smirnov test was used to evaluate a normal distribution. An independent-samples t-test was used to compare continuous variables between the two groups. The χ^2 test was used to compare categorical data. Entered factors included those with $P < 0.1$ in univariate analysis. Logistic regression analysis was used to identify predictors of ISR. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff values of the NLR. A probability (P) value of < 0.05 was considered statistically significant.

Results

We enrolled 199 patients to the present study, all of whom were followed up for more than 1 year, of whom 80 (40%) were determined as having ISR. There were 155 (77.9%) men and 44 (22.1%) women in this group. Patients were divided into two groups according to the occurrence of ISR within 1 year (group 1, ISR; group 2, Non-ISR). There was no difference between groups for age and sex distribution. There were 108 (54.3%) smoking, 50 (25.1%) coronary heart disease, and 112 (56.3%) hypertension patients although none were statistically different when comparing the

Table 1 Clinical and hematological characteristics of the according to development of in-stent restenosis

	ISR, n=80 (%)	Non-ISR, n=119 (%)	t	P value
Male	59 (73.7%)	96 (80.7%)	$\chi^2 = 1.33$	0.270
Age, Y	68.72 ± 11.37	70.59 ± 9.52	−1.256	0.211
Smoking	41 (51.2%)	67 (56.3%)	$\chi^2 = 0.492$	0.562
Hypertension	42 (52.5%)	70 (58.8%)	$\chi^2 = 0.770$	0.386
Diabetes mellitus	54 (67.5%)	61 (51.3%)	$\chi^2 = 5.170$	0.028
CAD	22 (27.5%)	28 (23.5%)	$\chi^2 = 0.400$	0.620
TASC II classification				
TASC A	3	4		0.980
TASC B	40	59		
TASC C	37	56		
Hematologic parameters				
Total cholesterol, mmol/l	4.40 ± 1.28	4.23 ± 1.19	0.929	0.354
Triglyceride, μmmol/l	1.76 ± 1.37	1.88 ± 1.78	−0.520	0.604
HDL, mmol/l	1.04 ± 0.30	1.04 ± 0.31	0.043	0.966
LDL, mmol/l	2.65 ± 0.95	2.39 ± 0.95	1.926	0.055
Bilirubin, μmol/l	12.1 ± 0.32	11.9 ± 0.13	0.930	0.422
Albumin, g/l	34.0 ± 1.31	33.5± 2.12	0.870	0.541
Hematologic parameters				
Pre-interventional monocyte count	0.51 ± 0.17	0.55 ± 0.31	−1.101	0.272
Post-interventional monocyte count	0.76 ± 0.28	0.68 ± 0.26	2.179	0.031
Pre-interventional eosinophil count	0.18 ± 0.19	0.18 ± 0.15	0.288	0.774
Post-interventional eosinophil count	0.20 ± 0.17	0.21 ± 0.25	−0.033	0.974
Pre-interventional basophils count	0.04 ± 0.02	0.03 ± 0.02	1.173	0.242
Post-interventional basophils count	0.03 ± 0.01	0.04 ± 0.05	−0.842	0.401
Pre-interventional leukocyte count	7.95 ± 1.88	8.34 ± 3.11	−0.996	0.320
Post-interventional leukocyte count	8.62 ± 2.66	8.17 ± 2.86	1.114	0.267
Pre-interventional platelet count	229.62 ± 77.83	232.02 ± 91.70	−0.192	0.848
Post-interventional platelet count	210.50 ± 69.40	215.75 ± 85.39	−0.458	0.647
Post-interventional PDW,%	16.91 ± 0.88	16.61 ± 1.18	1.899	0.059
Post-interventional PDW,%	18.24 ± 0.65	17.47 ± 3.61	1.868	0.063
Pre-interventional neutrophil count	5.32 ± 1.61	5.23 ± 1.65	0.366	0.715
Post-interventional neutrophil count	9.22 ± 1.07	5.80 ± 2.04	13.719	<0.001
Pre-interventional lymphocyte count	2.00 ± 0.64	1.82 ± 0.66	1.888	0.061
Post-interventional lymphocyte count	1.95 ± 0.41	1.70 ± 0.52	3.643	<0.001
NLR_{before}	2.87 ± 1.12	3.36 ± 1.99	−1.963	0.051
NLR_{after}	4.94 ± 1.35	3.65 ± 1.55	6.071	<0.001
NLR_{change}	2.07 ± 1.48	0.29 ± 1.86	7.136	<0.001
NLR_{ratio}	0.93 ± 0.80	0.31 ± 0.63	6.099	<0.001

Abbreviations: CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NLR, neutrophil–lymphocyte ratio.

ISR and no-restenosis groups ($P>0.05$). In addition, the TASC II classification of the femoral artery was not statistically different between the ISR and no-restenosis groups ($P>0.05$). χ^2 test analysis the diabetes mellitus statistically different between both groups ($P=0.028$). The post-interventional monocyte count was significantly different (ISR = 0.76 ± 0.28 vs Non-ISR = 0.68 ± 0.26, $P=0.031$). Although the before NLR was not different between the groups (ISR = 2.87 ± 1.12 vs Non-ISR = 3.36 ± 1.99, $P=0.051$), the NLR_{after} was significantly different (ISR = 4.94 ± 1.35 vs Non-ISR = 3.65 ± 1.55, $P<0.001$) and the NLR_{ratio} was significantly higher in Non-ISR (ISR = 4.94 ± 1.35 vs Non-ISR = 3.65 ± 1.55, $P<0.001$) (Table 1).

The predictors of ISR in the multivariate logistic regression analyses are presented in (Table 2). Because NLR_{after}, NLR change(NLR_{change}) and NLR_{ratio} were inflammatory markers, they were not considered together in the multivariate model. Therefore, three multivariate models including NLR_{after} (NLR_{after}, model 1), NLR_{change} (NLR_{change}, model 2) and NLR_{ratio} (NLR_{ratio}, model 3) were separately constructed. A $NLR_{after} > 4.3$ was associated with an odds ratio of 1.946 (95% CI [1.51–2.50]; $P<0.001$) for the presence of ISR. A $NLR_{change} > 1.24$ was associated with an odds ratio of 2.17 (95% CI [1.63–2.88]; $P<0.001$) for the presence of ISR; A NLR_{ratio} value >37.5% was associated with an

Table 2 Multivariate analysis of predictors of ISR after superficial femoral artery stenting

Variables	Model 1 (NLR_{after})		Model 2 (NLR_{change})		Model 3 (NLR_{ratio})	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Post-interventional monocyte count	1.294 (0.38–4.35)	0.677	1.81 (0.52–6.33)	0.350	2.18 (0.67–7.05)	0.192
Pre-interventional lymphocyte count	2.272 (1.33–3.86)	0.003	0.80 (0.46–1.38)	0.437	0.78 (0.44–1.36)	0.389
LDL	1.275 (0.89–1.75)	0.182	1.43 (1.02–2.01)	0.037	1.36 (0.98–1.89)	0.059
Pre-interventional PDW	1.116 (0.79–1.55)	0.522	1.16 (0.82–1.66)	0.384	1.18 (0.84–1.64)	0.326
Post-interventional PDW	1.07(0.95–1.21)	0.251	1.05 (0.92–1.20)	0.453	1.05 (0.91–1.21)	0.463
Diabetes mellitus	0.59(0.30-1.19)	0.144	0.73 (0.36–1.47)	0.383	0.72 (0.37–1.42)	0.354
NLR_{change}	—		2.17 (1.63–2.88)	<0.001	—	
NLR_{ratio}	—		—		3.6 (2.03–6.36)	<0.001
NLR_{after}	1.946 (1.51–2.50)	<0.001	—		—	

Abbreviations: LDL, low-density lipoprotein; NLR, neutrophil–lymphocyte ratio; PDW, platelet distribution width.
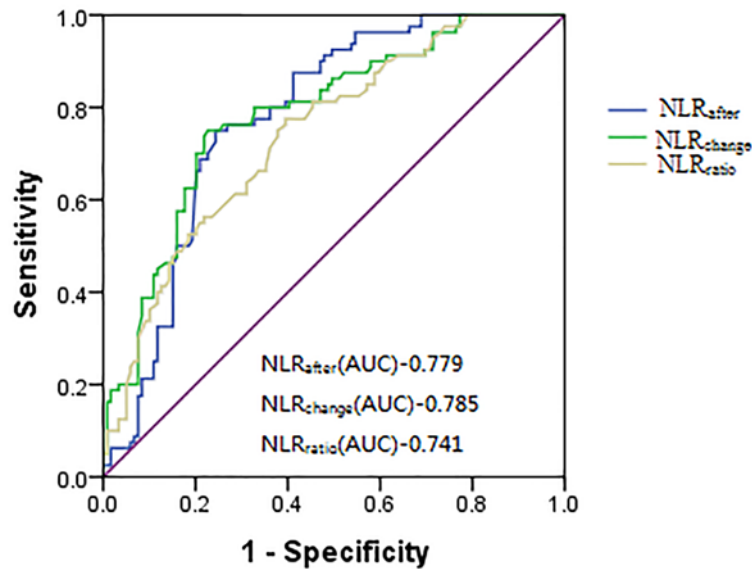

Figure 1. The ROC curves of NLR_{after}, NLR_{change} and NLR_{ratio} were not significantly different, and the clinical diagnostic efficacy was almost the same
NLR, Neutrophil–lymphocyte ratio.

odds ratio of 3.6 (95% CI [2.03–6.36]; *P*<0.001) for the occurrence of ISR. Among these, NLR_{ratio} was found to be significant independent predictor of ISR in the multivariate logistic regression analysis. Pearson's correlation analysis showed that NLR_{ratio} was positively correlated with the onset time of ISR ($r = 0.41$; *P*<0.001).

A NLR_{after} level > 4.3 predicted ISR with 75% sensitivity and 76% specificity for the prediction of ISR, as identified by the ROC curve. The area under the ROC curve (AUC) was 0.779 (95% CI [0.71–0.84], *P*<0.001). A NLR_{change} level > 1.24 predicted ISR with 75% sensitivity and 77% specificity, AUC was 0.785 (95% CI [0.72–0.85], *P*<0.001). A NLR_{ratio} level > 37.5% had 77% sensitivity and 60% specificity. AUC was 0.741 (95% CI [0.67–0.81], *P*<0.001). The ROC curves of NLR_{after}, NLR_{change} and NLR_{ratio} were not significantly different, and the clinical diagnostic efficacy was almost the same. The ROC curve comparison of these three markers is shown in Figure 1.

Discussion

Atherosclerosis is a progressive, complex and multifactorial disease. Inflammation plays an important role in all stages of the atherosclerosis development [13,14]. ISR has been attributed to neointimal hyperplasia in the early stage after the procedure [15]. Inflammatory cells may accelerate neointimal hyperplasia because of their release of growth and

chemotactic factors [16] or production of enzymes (e.g. matrix metalloproteinases), which can degrade extracellular constituents and facilitate cell migration [17,18]. Neutrophils respond to different inflammatory stimuli resulting in release of various cytokines and cytotoxic/proteolytic enzymes that affect the vascular system by numerous mechanisms such as induction of damage to endothelial cells, induction of the coagulation system [19]. Lymphocyte count reflects a physiologic stress response to cortisol [20]. The NLR has been shown to be a marker of inflammation and closely related to increased cardiovascular mortality and morbidity [5,6]. The primary finding of our study is that the NLR_{ratio} level was a better independent predictor than NLR_{after} level for the occurrence of the ISR in patients who underwent superficial femoral artery stenting for lower extremity arteriosclerosis obliterans.

Our study observed that in patients presenting with restenosis within 12 months, the NLR increased after stent implantation. We find a positive correlation between the NLR_{ratio} and an occurrence of ISR ($r=0.41$; $P<0.001$). Patients with a NLR_{ratio} value > 37.5% had a 3.47-fold higher risk of ISR when compared with a NLR_{ratio} value < 37.5%. Patients with a NLR_{after} value > 4.3 had a 1.96-fold higher risk of ISR when compared with a NLR_{after} value < 4.3. Moreover, patients with a NLR_{change} > 1.24 had a 2.13-fold higher risk of ISR than did patients with a NLR_{change} value < 1.24. A NLR_{ratio} level > 37.5% had 77% sensitivity and 60% specificity for the prediction of ISR, A NLR_{change} level > 1.24 predicted ISR with 75% sensitivity and 77% specificity. The NLR_{change} in our study is higher than that reported in most other studies. For example, Balli et al. [21] reported the neutrophil–lymphocyte ratio for prediction of in-stent restenosis in coronary stents. A NLR_{change} level > 0.58 had 81.8% sensitivity and 93.5% specificity for the prediction of ISR. This discrepancy might be caused by the different lesion sites studied. The superficial femoral artery stent might be affected by the compression, pulling and torsion of the thigh muscle, resulting in continuous vascular damage, while the coronary arteries are less affected by the muscle. Chang et al. [10] reported that the NLR_{before} > 3.62 was independently and positively associated with a higher risk of early (within 1 year) ISR after stent implantation in patients with femoropopliteal chronic total occlusion. His results differ from ours in that we did not find a relationship between the NLR_{before} levels and the occurrence of ISR. The differences may be: first, we excluded patients with active infection, chronic inflammation, malignancy, and copd. Inflammation is considered to play a key role in the pathophysiological process for many chronic diseases. Second, they mainly studied the chronic complete occlusion of femoral popliteal artery, while we mainly studied the superficial femoral artery, and the patients did not have severe limb ischemia. In addition, the relationship between post-operative NLR and stent restenosis has not been analyzed.

Occurrence of ISR is a complex and multifactorial process [22]. Inflammation appears to be one of the many risk factors for stent restenosis [22,23]. The inflammatory process plays an important role not only in initiation and progression of atherosclerosis [14] but also in development of stent restenosis [24,25]. In general, the inflammation process contributes to stent restenosis by two distinct mechanisms, namely local vascular inflammation because of mechanical injury inflicted by stent implantation [24] and a pre-existing systemic inflammatory state before the procedure. [22,23]. The association between systemic inflammation and ISR has been reported in various studies conducted on different inflammatory markers. Of those, CRP was the most frequently studied biomarker owing to its accurately reflecting systemic inflammation [26] and being a strong predictor of cardiovascular outcomes [27]. Our research is mainly discussed because of mechanical damage caused by stent implants, namely, local vascular inflammation. Donners reported that [3] depending on endothelial damage during the PCI, increases in adhesive molecules and chemotactic factors are followed by the accumulation of inflammatory cells and pro-inflammatory molecules, such as interleukin-1 and 6, which mediate the development of neointimal proliferation. In our study, NLR_{ratio} was stronger independent predictors of short-term survival than other leukocytes. The predictive superiority of NLR may be due to 1 factor, NLR is a ratio of two different yet complementary immune pathways. Neutrophils are responsible for active ongoing nonspecific inflammation through secretion of many inflammatory mediators, like elastase [28], myeloperoxidase [29] and oxygen free radicals that can facilitate plaque disruption. An increase in neutrophil count predicts an increase in neointima and undesirable outcomes of stent restenosis. Lymphocytes, in contrast, represent the regulatory pathway of the immune system. CD4, the main subtype of total lymphocyte count, reflects a physiologic stress response to cortisol [20].The neutrophil–lymphocyte ratio therefore reflects both the neutrophil of inflammation and the relative lymphocyte of cortisol-induced stress response. In consequence, high NLR reflects two different immune pathways; hence, it is more predictive than either parameter alone.

In addition, we found that the proportion of diabetic patients in ISR group was significantly higher than that in non-ISR group, and the difference between ISR group and non-ISR group was significant. Diabetes mellitus has been shown to be an important risk factor for poor prognosis in patients with cardiovascular interventional therapy [30]. This is consistent with our observation that diabetes is an important factor for poor prognosis after superficial femoral artery stent implantation, but our findings suggest that diabetes is not an independent risk factor for ISR.

Our study has several limitations. This study was conducted on a retrospective basis and represented a single center experience. Second, the limitations of our study were the small sample, which we recognize might lead to differences in some of the reported observations.

In conclusion, NLR_{ratio} could be used as an inexpensive and easy-to-access method for assessment of inflammatory status and prognosis in patients with superficial femoral artery stents.

Highlights

(1) Determine the risk factors of restenosis in superficial femoral artery stents early in clinical treatment by simple and convenient examination methods.

(2) Evaluate the studies that investigating NLR_{ratio} and to identify the prognostic and diagnostic value of NLR_{ratio} as an inexpensive and easy-to-access parameter after superficial femoral artery stents.

(3) The new findings of this work have deepened the current understanding of in-stent restenosis in the superficial femoral artery and provide a theoretical basis for the prevention of ISR. As such the findings are valuable for future studies.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Funding

Author Contribution

Liang Xiao initiated the project and designed the experiment. Yaobo Yang, Fangfang Ge and Jing Shen Jianbo Song conducted clinical data collection. Yaobo Yang, Jiapei Xie, Jiangshuai Qu, Xinzu Mao and Zhao-cheng Kuang performed postoperative follow-up and recorded data. Xiang Wang and Yejun Wu conducted a number of collation and statistical analysis. Yaobo Yang wrote the original manuscript. Liang Xiao and Shenghai Wang revised the paper. All authors reviewed and approved the paper.

Abbreviations

CAD, coronary artery disease; HDL, high-density lipoprotein; ISR, in-stent restenosis; LDL, low-density lipoprotein; NLR, neutrophil–lymphocyte ratio; PDW, platelet distribution width.

References

1 Norgren, L., Hiatt, W.R., Dormandy, J.A. et al. (2007) Inter-society consensus for the management of peripheral arterial disease (TASC II). *J. Vasc. Surg.* **45**, S5–S67, https://doi.org/10.1016/j.jvs.2006.12.037

2 Razzouk, L., Aggarwal, S., Gorgani, F. and Babaev, A. (2013) In-stent restenosis in the superficial femoral artery. *Ann. Vasc. Surg.* **27**, 510–524, https://doi.org/10.1016/j.avsg.2012.09.005

3 Donners, M.M., Daemen, M.J., Cleutjens, K.B. and Heeneman, S. (2003) Inflammation and restenosis: implications for therapy. *Ann. Med.* **35**, 523–531, https://doi.org/10.1080/07853890310014876

4 Joviliano, E.E., Piccinato, C.E., Dellalibera-Joviliano, R., Moriya, T. and E'vora, P.R. (2011) Inflammatory markers and restenosis in peripheral percutaneous angioplasty with intravascular stenting: current concepts. *Ann. Vasc. Surg.* **25**, 846–855, https://doi.org/10.1016/j.avsg.2011.02.026

5 Tamhane, U.U., Aneja, S., Montgomery, D., Rogers, E.K., Eagle, K.A. and Gurm, H.S. (2008) Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am. J. Cardiol.* **102**, 653–657, https://doi.org/10.1016/j.amjcard.2008.05.006

6 Papa, A., Emdin, M., Passino, C., Michelassi, C., Battaglia, D. and Cocci, F. (2008) Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. *Clin. Chim. Acta* **395**, 27–31, https://doi.org/10.1016/j.cca.2008.04.019

7 Ferrante, G., Niccoli, G., Biasucci, L.M., Liuzzo, G., Burzotta, F., Galiuto, L. et al. (2008) Association between C-reactive protein and angiographic restenosis after bare metal stents: an updated and comprehensive meta-analysis of 2747 patients. *Cardiovasc. Revasc. Med.* **9**, 156–165, https://doi.org/10.1016/j.carrev.2008.01.003

8 Rahel, B.M., Visseren, F.L., Suttorp, M.J., Plokker, T.H., Kelder, J.C., de Jongh, B.M. et al. (2003) Preprocedural serum levels of acute phase reactants and prognosis after percutaneous coronary intervention. *Cardiovasc. Res.* **60**, 136–140, https://doi.org/10.1016/S0008-6363(03)00355-9

9 Turak, O., Ozcan, F., Isleyen, A., Tok, D., Sokmen, E., Buyukkaya, E. et al. (2012) Usefulness of the neutrophil-to-lymphocyte ratio to predict bare-metal stent restenosis. *Am. J. Cardiol.* **110**, 1405–1410, https://doi.org/10.1016/j.amjcard.2012.07.003

10 Chang, Z., Zheng, J., Guo, Q. et al. (2018) The Relationship Between the Neutrophil-Lymphocyte Ratio and In-Stent Restenosis in Patients with Femoropopliteal Chronic Total Occlusions. *Angiology* **69**, 1–6

11 Hirsch, A.T., Haskal, Z.J., Hertzer, N.R. et al. (2006) ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* **113**, e463–e654

12 Bray, P.J., Robson, W.J. and Bray, A.E. (2003) Percutaneous treatment of long superficial femoral artery occlusive disease: efficacy of the Hemobahn stent-graft. *J. Endovasc.Ther.* **10**, 619–628, https://doi.org/10.1177/152660280301000331

13 Tannd, A., Erkan, A.F., Ekici, B., Alhan, A. and Töre, H.F. (2014) Neutrophil to lymphocyte ratio is associated with more extensive, severe and complex coronary artery disease and impaired myocardial perfusion. *Türk Kardiyol Dern Ars* **42**, 125–130, https://doi.org/10.5543/tkda.2014.18949

14 Libby, P. (2002) Inflammation in atherosclerosis. *Nature* **420**, 868–874, https://doi.org/10.1038/nature01323

15 Goel, S.A., Guo, L.W., Liu, B. and Kent, K.C. (2012) Mechanisms of post-intervention arterial remodelling. *Cardiovasc. Res.* **96**, 363–371, https://doi.org/10.1093/cvr/cvs276

16 Assoian, R.K., Fleurdelys, B.E., Stevenson, H.C., Miller, P.J., Madtes, D.K., Raines, E.W. et al. (1987) Expression and secretion of type beta transforming growth factor by activated human macrophages. *Proc. Natl. Acad. Sci. U.S.A.* **84**, 6020–6024, https://doi.org/10.1073/pnas.84.17.6020

17 Garbisa, S., Ballin, M., Daga-Gordini, D., Fastelli, G., Naturale, M., Negro, A. et al. (1986) Transient expression of type IV collagenolytic metalloproteinase by human mononuclear phagocytes. *J. Biol. Chem.* **261**, 2369–2375

18 Sukhova, G.K., Shi, G.P., Simon, D.I., Chapman, H.A. and Libby, P. (1998) Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells. *J. Clin. Invest.* **102**, 576–583, https://doi.org/10.1172/JCI181

19 Spark, J.I., Sarveswaran, J., Blest, N., Charalabidis, P. and Asthana, S. (2010) An elevated neutrophil-lymphocyte ratio independently predicts mortality in chronic critical limb ischemia. *J. Vasc. Surg.* **52**, 632–636, https://doi.org/10.1016/j.jvs.2010.03.067

20 Blum, A., Sclarovsky, S., Rehavia, E. and Shohat, B. (1994) Levels of T-lymphocyte subpopulations, interleukin-1beta, and soluble interleukin-2 receptor in acute myocardial infarction. *Am. Heart J.* **127**, 1226–1230, https://doi.org/10.1016/0002-8703(94)90040-X

21 Balli, M., Taşolar, H., Çetin, M. et al. (2015) Use of the neutrophil to lymphocyte ratio for prediction of in-stent restenosis in bifurcation lesions. *Eur. Rev. Med. Pharmacol. Sci.* **19**, 1866–1873

22 Jukema, J.W., Verschuren, J.J., Ahmed, T.A. and Quax, P.H. (2011) Restenosis after PCI. Part 1: Pathophysiology and risk factors. *Nat. Rev. Cardiol.* **9**, 53–62, https://doi.org/10.1038/nrcardio.2011.132

23 Li, J.J., Nie, S.P., Zhang, C.Y., Gao, Z., Zheng, X. and Guo, Y.L. (2007) Is inflammation a contributor for coronary stent restenosis? *Med. Hypotheses* **68**, 945–951, https://doi.org/10.1016/j.mehy.2006.05.069

24 Inoue, T., Croce, K., Morooka, T., Sakuma, M., Node, K. and Simon, D.I. (2011) Vascular inflammation and repair implications for re-endothelialization, restenosis, and stent thrombosis. *JACC Cardiovasc. Interv.* **4**, 1057–1066, https://doi.org/10.1016/j.jcin.2011.05.025

25 Akpek, M., Kaya, M.G., Uyarel, H., Yarliogues, M., Kalay, N., Gunebakmaz, O. et al. (2011) The association of serum uric acid levels on coronary flow in patients with STEMI undergoing primary PCI. *Atherosclerosis* **219** 334–341, https://doi.org/10.1016/j.atherosclerosis.2011.07.021

26 Niccoli, G., Montone, R.A., Ferrante, G. and Crea, F. (2010) The evolving role of inflammatory biomarkers in risk assessment after stent implantation. *J. Am. Coll. Cardiol.* **56**, 1783–1793, https://doi.org/10.1016/j.jacc.2010.06.045

27 Ridker, P.M., Rifai, N., Rose, L., Buring, J.E. and Cook, N.R. (2002) Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N. Engl. J. Med.* **347**, 1557–1565, https://doi.org/10.1056/NEJMoa021993

29 Mehta, J., Dinerman, J., Mehta, P., Saldeen, T.G., Lawson, D., Donnelly, W.H. et al. (1989) Neutrophil function in ischemic heart disease. *Circulation* **79**, 549–556, https://doi.org/10.1161/01.CIR.79.3.549

29 Baldus, S., Heeschen, C., Meinertz, T., Zeiher, A.M., Eiserich, J.P., Munzel, T. et al. (2003) Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation* **108**, 1440–1445, https://doi.org/10.1161/01.CIR.0000090690.67322.51

30 Van Belle, E., Ketelers, R., Bauters, C. et al. (2001) Patency of percutaneous transluminal coronary angioplasty sites at 6-month angiographic follow-up: a key determinant of survival in diabetics after coronary balloon angioplasty. *Circulation* **103**, 1218–1224, https://doi.org/10.1161/01.CIR.103.9.1218